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Moderation of dietary sodium potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers

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Dietary sodium restriction has been shown to enhance the short-term response of blood pressure and albuminuria to angiotensin receptor blockers (ARBs). Whether this also enhances the long-term renal and cardiovascular protective effects of ARBs is unknown. Here we conducted a *post-hoc* analysis of the RENAAL and IDNT trials to test this in patients with type 2 diabetic nephropathy randomized to ARB or non-renin–angiotensin–aldosterone system (non-RAASi)–based antihypertensive therapy. Treatment effects on renal and cardiovascular outcomes were compared in subgroups based on dietary sodium intake during treatment, measured as the 24-h urinary sodium/creatinine ratio of 1177 patients with available 24-h urinary sodium measurements. ARB compared to non-RAASi–based therapy produced the greatest long-term effects on renal and cardiovascular events in the lowest tertile of sodium intake. Compared to non-RAASi, the trend in risk for renal events was significantly reduced by 43%, not changed, or increased by 37% for each tertile of increased sodium intake, respectively. The trend for cardiovascular events was significantly reduced by 37%, increased by 2% and 25%, respectively. Thus, treatment effects of ARB compared with non-RAASi–based therapy on renal and cardiovascular outcomes were greater in patients with type 2 diabetic nephropathy with lower than higher dietary sodium intake. This underscores the avoidance of excessive sodium intake, particularly in type 2 diabetic patients receiving ARB therapy.

Kidney International (2012) **82,** 330–337; doi:10.1038/ki.2012.74; published online 21 March 2012

KEYWORDS: angiotensin receptor blockers; diabetic nephropathy; dietary sodium; type 2 diabetes

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Received 28 September 2011; revised 17 December 2011; accepted 3 January 2012; published online 21 March 2012

Agents intervening in the renin–angiotensin–aldosterone system (RAASi) are considered a mainstay of therapy in the prevention of end-stage renal and cardiovascular disease in patients with diabetes, both in early and late stage of disease.[1–4] Despite proven efficacy of RAASi, it is known that the risk of renal and cardiovascular disease remains high in a substantial number of patients.[5] The high risk of renal and cardiovascular disease is closely linked to high residual blood pressure and albuminuria. To address this high residual risk, further reduction of blood pressure and albuminuria may be required. One of the options is to optimize the efficacy of RAASi.

Several studies have consistently demonstrated that dietary sodium restriction enhances the blood pressure and albuminuria response to angiotensin receptor blockers (ARBs) in both diabetic and nondiabetic patients with chronic kidney disease.[6,7] However, these studies were short in duration and did not assess whether dietary sodium restriction potentiates the long-term effects of ARBs on hard renal or cardiovascular outcomes. In fact, some claim that dietary sodium restriction by itself may enhance the long-term risk for renal and/or cardiovascular disease in diabetic patients.[8]

The purpose of the present study was to determine whether a low-sodium diet, as indicated by low urinary sodium excretion, increases the efficacy of an ARB on hard renal and cardiovascular end points in type 2 diabetic patients with nephropathy. To this end, data of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) trials were merged and analyzed.

RESULTS

Characteristics of the study population

Table 1 shows the characteristics of the overall population and by tertiles of sodium/creatinine ratio. Participants included in the current report share the characteristics of the overall RENAAL and IDNT population.[1,2] Mean 24-h sodium/creatinine ratio was 142 (±69) mmol/g and mean

Table 1 | Characteristics of the overall population and stratified according to tertiles of 24-h urinary sodium/creatinine ratio

Variable	Overall	Stratified by sodium/creatinine ratio		
Tertiles		1	2	3
Sodium intake range[a]		<121	121–153	⩾153
N	1177	392	393	392
ARB assigned treatment, *N*	499	173	175	151
Age (years)	59 (8)	59 (8.0)	60 (7.8)	59 (8.0)
Gender (*n*, % female)	408 (34.7)	82 (20.9)	142 (36.1)	182 (46.9)[b]
Race (n, %)				
White	579 (49.2)	168 (42.8)	197 (50.1)	214 (54.6)[b]
Black	293 (24.9)	145 (37.0)	98 (24.9)	50 (12.8)[b]
Hispanic	240 (20.4)	62 (15.8)	76 (19.3)	102 (26.0)[b]
Asian	46 (3.9)	13 (3.3)	14 (3.6)	19 (4.9)
Others	19 (1.6)	4 (1.0)	8 (2.0)	7 (1.8)
Systolic BP (mm Hg)	154.9 (21)	153.1 (21)	155.7 (20)	156.0 (21)
Diastolic BP (mm Hg)	83.6 (11)	84.2 (12)	83.2 (11)	83.4 (11)
Serum creatinine (mg/dl)	1.8 (0.5)	1.9 (0.5)	1.8 (0.5)	1.8 (0.6)
eGFR (ml/min per 1.73 m^2)	44.0 (16)	45.6 (16.7)	44.1 (15.3)	42.2 (16.5)[b]
HbA1c (%)	8.5 (1.7)	8.4 (1.6)	8.4 (1.6)	8.8 (1.8)
Hemoglobin (mg/dl)	12.5 (2.0)	12.8 (1.9)	12.5 (2.0)	12.4 (1.9)[b]
Total cholesterol (mg/dl)	225 (57)	210 (57)	222 (52)	232 (59)
Serum albumin (mg/dl)	3.8 (0.5)	3.8 (0.4)	3.8 (0.5)	3.7 (0.5)
Body weight (kg)	89.0 (22)	91.9 (21)	89.8 (23)	85.4 (23)[b]
Body mass index (kg/m^2)	31.2 (6.7)	31.0 (6.3)	31.6 (6.9)	30.9 (6.9)
Urinary albumin excretion (mg/24 h)	1897 (942–3815)	1824 (901–3806)	1765 (947–3450)	2251 (963–3929)
Urinary creatinine excretion (g/24 h)	1.4 (0.6)	1.6 (0.6)	1.4 (0.6)	1.2 (0.4)[b]
Urinary albumin/creatinine ratio (mg/g)	1554 (775–2946)	1173 (639–2617)	1533 (783–2656)	1905[b] (910–3675)
Urinary sodium excretion (mmol/24-h)	181 (86)	152 (76)	179 (82)	209 (90)
Urinary sodium/creatinine ratio (mmol/g; based on 24-h)	142 (69)	99 (34)	134 (39)	192 (85)[b]
Urinary urea excretion (g/24-h)[c]	9.8 (4.0)	10.3 (4.1)	9.6 (3.9)	9.4 (4.0)
Diuretic use (*n*, %)	720 (61)	233 (59.4)	225 (57.3)	262 (66.8)
β-Blocker use (*n*, %)	190 (16)	67 (17.1)	60 (15.3)	63 (16.1)
Calcium antagonist use (*n*, %)	683 (58)	226 (57.7)	233 (59.3)	224 (57.1)

Abbreviations: ARB, angiotensin receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate.
[a]Ranges are indicated for 24-h sodium/creatinine ratio (mmol/g).
[b]$P<0.05$ for tests for trends across urinary/sodium excretion tertiles.
[c]Data are provided from subjects participating in the IDNT trial in whom urinary urea excretion was measured.
Values are expressed as mean with standard deviation. Urinary albumin excretion and urinary albumin/creatinine ratio is expressed as median with interquartile ranges.

urinary sodium excretion was 181 (±86) mmol/24 h. Participants in the upper tertile of 24-h sodium/creatinine ratio were more likely to be women, less likely to be of black ethnicity, had a higher 24-h urinary albumin/creatinine ratio, and a slightly but statistically significantly lower estimated glomerular filtration rate (eGFR) and hemoglobin level (Table 1).

Effects of angiotensin receptor blockade on albuminuria and blood pressure by urinary sodium/creatinine ratio

ARB treatment compared with non-RAASi–based antihypertensive therapy produced the greatest effects on albuminuria and systolic blood pressure in participants in the lowest tertile of 24-h urinary sodium/creatinine ratio (Table 2). Similar results were observed when the population was stratified according to another measure of sodium intake, namely 24-h urinary sodium excretion (Supplementary Table S1 online).

Relationship between urinary sodium/creatinine ratio and renal and cardiovascular events

A total of 372 subjects experienced a renal event and 392 subjects experienced a cardiovascular event during follow-up.

Table 2 | Albumin/creatinine ratio and systolic blood pressure response to ARB therapy compared with non-RAASi-based therapy at month 6 according to tertiles of 24-h urinary sodium/creatinine ratio

	6-Month response (95% confidence interval)	
24-h Urinary sodium/creatinine ratio (mmol/g)	24-h ACR response (%)	Systolic BP response (mm Hg)
<121	−44 (−55 to −30)	−5.0 (−8.8 to −1.1)
121–153	−16 (−32 to +3)	−4.6 (−8.3 to −1.0)
⩾153	−21 (−35 to −2)	−3.5 (−7.4 to +0.4)

Abbreviations: ACR, albumin to creatinine ratio; ARB, angiotensin receptor blocker; BP, blood pressure; non-RAASi, non-renin–angiotensin–aldosterone system.

Figure 1 shows the Kaplan–Meier survival estimates for renal and cardiovascular events in subjects treated with ARB and non-RAASi–based therapy by tertiles of 24-h sodium/creatinine ratio. Sodium/creatinine ratio did not determine the renal or cardiovascular outcome of subjects in the non-RAASi–based therapy group. In ARB-treated subjects, however, renal and cardiovascular events decreased across decreasing tertiles of 24-h sodium/creatinine ratio.

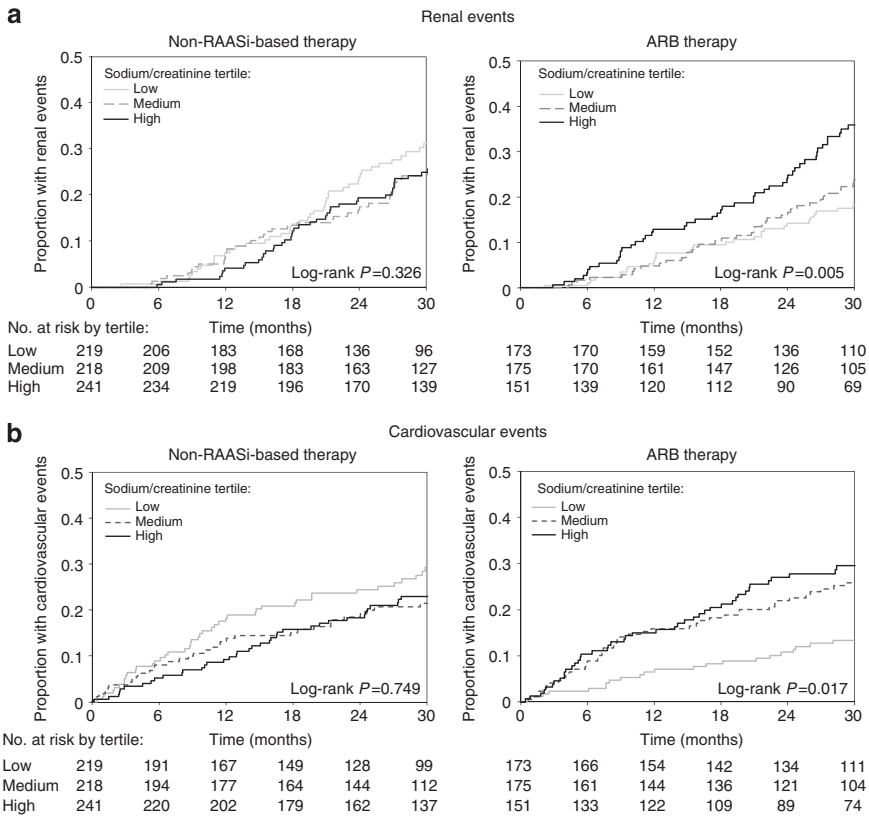

Figure 1 | Kaplan–Meier curves according to tertiles of 24-h urinary sodium/creatinine ratio. Kaplan–Meier curves for (**a**) renal and (**b**) cardiovascular events in subjects who received angiotensin receptor blocker (ARB)– and non-renin–angiotensin–aldosterone system (non-RAASi)–based therapy stratified by tertiles of 24-h sodium/creatinine ratio: <121 mmol/g; 121–153 mmol/g; ⩾153 mmol/g.

Effects of angiotensin receptor blockade on renal and cardiovascular events by urinary sodium/creatinine ratio

Compared with non-RAASi–based therapy, treatment with ARBs resulted in greater relative effects on renal and cardiovascular events in subjects in the lowest tertile of 24-h sodium/creatinine ratio (*P*-value for trend <0.001 for renal events and 0.021 for cardiovascular events; Figure 2). A trend toward greater relative risk reductions for hospitalization for heart failure events was observed in participants in the lowest tertile of 24-h sodium/creatinine ratio (Figure 2). An analysis that stratified the population according to 24-h urinary sodium excretion provided nearly identical results: the relative risk reductions for renal events in the lowest vs. highest tertile of 24-h urinary sodium excretion were 25% (hazard ratio (HR): 0.75, 95% confidence interval (CI): 0.53–1.05) vs. −27% (HR: 1.27, 95% CI: 0.86–1.88) and for cardiovascular events 10% (HR: 0.90, 95% CI: 0.65–1.22) vs. −3% (HR: 1.03, 95% CI: 0.73–1.46). An additional analysis that excluded amlodipine-assigned patients in the IDNT trial provided comparable results (Supplementary Figure S1 online). Similarly, the results were not different from the main analyses when irbesartan was compared with amlodipine in the IDNT trial (Supplementary Figure S2 online). A sensitivity analyses stratifying the population for baseline 24-h sodium/creatinine ratio showed the same trend as the main analyses with greater ARB treatment effects in subjects in the lowest tertile of 24-h sodium/creatinine ratio (Supplementary Table S2 online). Further analyses adjusting the relative treatment effects for estimated GFR or urinary urea excertion provided essentially similar results underscoring the robustness of the findings.

The effects of ARB treatment on the course of estimated GFR decline is shown in Figure 3. Participants receiving ARB therapy in the lowest tertile of 24-h sodium/creatinine ratio had a significantly slower rate of renal function decline compared with non-RAASi treatment: 4.4 (95% CI: 3.6–5.1) vs. 5.7 (5.0–6.4) ml/min per 1.73 m^2; $P = 0.010$. No difference in the rate of eGFR decline was observed between ARB and non-RAASi–based therapy in the upper two tertiles of 24-h sodium/creatinine ratio (Figure 3).

DISCUSSION

The results of this study demonstrate that the reductions in the relative risk of renal and cardiovascular events achieved with ARB therapy in type 2 diabetic patients with nephropathy are larger in subjects with lower dietary sodium intake (estimated from 24-h urinary sodium/creatinine ratio). The renal and cardiovascular protective effects of ARB therapy compared with non-RAASi–based therapy attenuated in subjects with larger consumption of sodium so that in subjects with

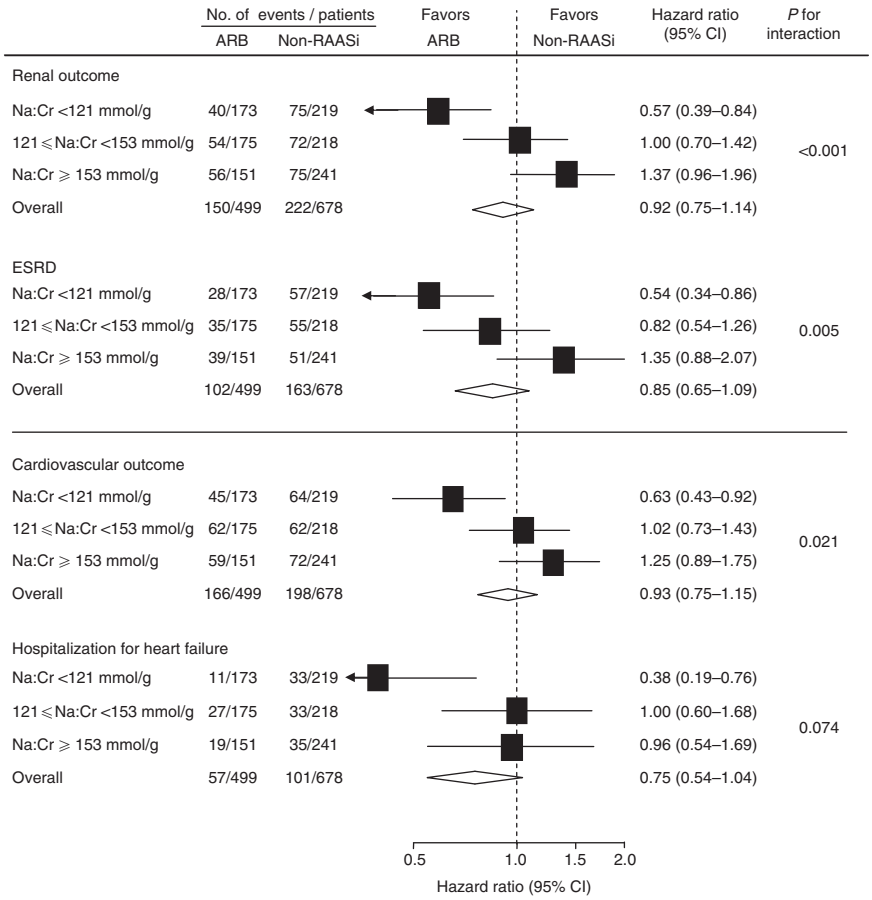

Figure 2 | Effect of angiotensin receptor blocker (ARB) treatment vs. non-renin–angiotensin–aldosterone system (non-RAASi)–based treatment on the risk for renal and cardiovascular outcomes according to tertiles of 24-h urinary sodium/creatinine ratio. The center of the diamond represents the overall estimate, and the width represents its 95% confidence interval (CI). Solid boxes represent estimates of treatment effects in subgroups, and the horizontal line represents the 95% CI. ESRD, end-stage renal disease.

the highest sodium intake the treatment effects on hard renal and cardiovascular outcomes were completely annihilated.

Treatment guidelines for patients with chronic disease recommend dietary salt intake of less than 5–6 g per day, which approximately equals less than 100 mmol of sodium excretion per day.[9,10] Unfortunately, a dietary sodium intake of 5–6 g per day appears difficult to achieve. In our cohort, average sodium excretion was 142 mmol per g creatinine or 181 mmol per day, which equals a sodium intake of ~11 g per day, well above the recommended limit. Similar values were reported in other large intervention trials such as the REIN I and II cohorts (approximately 170 mmol per day and 200 mmol per day), and the AASK trial (150 mmol per day).[11–13] Interestingly, the greater treatment effects in subjects within the lowest tertile of dietary sodium intake were already observed in subjects with a liberal sodium intake of 99 mmol per g creatinine, equivalent to 152 mmol of sodium per day, or 8.8 g of salt per day. These data support the clinical applicability of our findings and underscore global efforts to avoid excessively high sodium intake.

The data on a direct relationship, irrespective of drug treatment, between dietary sodium intake and morbidity and mortality are limited and inconclusive. A Finnish study in the general population showed that a high salt intake (judged by urinary sodium excretion) increased the risk of coronary heart disease mortality, cardiovascular disease mortality, and all-cause mortality, especially in obese but not in non-obese individuals.[14] These findings were confirmed in the US general population. Data from the third National Health and Nutrition Examination Survey demonstrated that each gram per day increment in sodium intake (estimated from 24-h dietary recall) was associated with a 20% higher risk for all-cause mortality.[15] In addition, long-term follow-up data from the Trials of Hypertension Prevention reported that subjects allocated to the dietary sodium intervention arm experienced a 25% lower risk on cardiovascular events during 10–15 years of follow-up.[16] Another study recently reported that renal function decline was slower among women with low than with high dietary sodium intake.[17] In contrast, Ekinci recently reported that lower sodium intake was independently associated with a higher risk for cardiovascular and all-cause mortality in individuals with type 2 diabetes.[8] However, the population may not be representative for all type 2 diabetics, as high blood pressure in this population

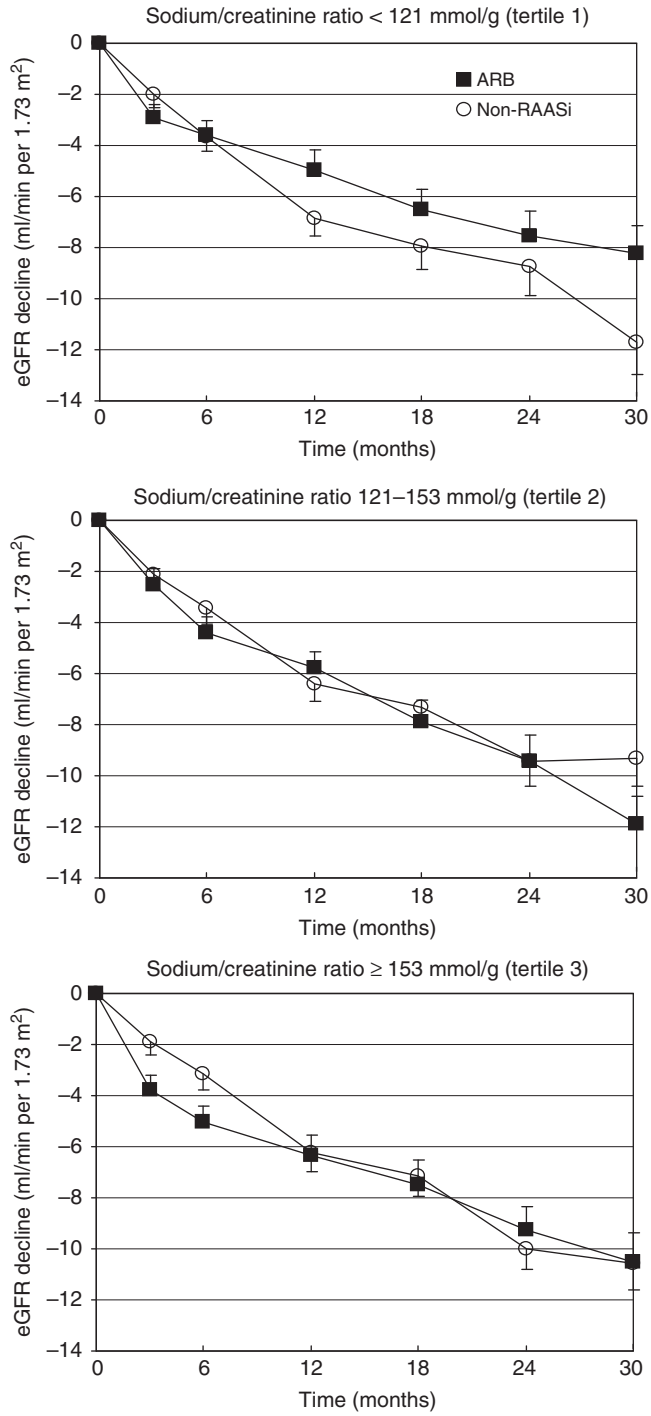

Figure 3 | Mean estimated glomerular filtration rate (eGFR) levels through 30 months among patients who were assigned to receive angiotensin receptor blocker (ARB) or non-renin–angiotensin–aldosterone system (non-RAASi)–based therapy by tertiles of 24-h sodium/creatinine ratio.

was also paradoxically associated with a decreased risk for mortality. Nevertheless, another recent population-based cohort study reported that lower dietary sodium intake (assessed by single 24-h urine collection) was associated with increased risk for cardiovascular mortality.[18] Our data did not reveal any association between measures of dietary sodium intake and renal or cardiovascular outcome in non-RAASi-treated individuals either in non-adjusted or adjusted analyses. The varying results on the association between dietary sodium intake and hard outcomes are probably best explained by the observational nature of all of these studies, including our study, and the different methodologies to estimate dietary sodium intake (i.e., dietary recall as opposed to urinary sodium excretion and single vs. multiple urinary sodium measurements). This may have led to unmeasured confounding and different effects of various populations with different dietary patterns. Thus, although various studies attempt to delineate the relationship between changes in salt intake and clinical outcomes, they should be interpreted as hypothesis generating. Randomized controlled trials are needed to truly assess the impact of salt reduction on morbidity and mortality.

Far better are the short-term studies on the impact of restricting dietary sodium intake on blood pressure and albuminuria responses during RAASi.[6,7,19] No long-term hard outcome data are, however, available on the effects of RAASi during a low-salt diet in diabetic patients. A recent *post-hoc* analysis of the REIN I and II trials in 500 subjects with nondiabetic nephropathy demonstrated a threefold larger reduction in the risk of end-stage renal disease during ramipril therapy in those with low compared with high urinary sodium excretion.[20] However, analyses from the REIN cohorts solely included patients receiving ramipril. Importantly, no correction could be made for placebo effects, rendering it impossible to correct for the fact that there might be a reason why some people ate more or less salt. By contrast, in the current study, the effects of ARB treatment on renal and cardiovascular events were based on non-RAASi–based controlled comparisons. In addition, the REIN data can only be applied to individuals with nondiabetic nephropathies. Because of differences in etiology between diabetic and nondiabetic renal diseases, it is uncertain whether these findings could be generalized to the broader population of patients with diabetes. Our study suggests that a liberal guideline-recommended dietary sodium intake during RAAS blockade is beneficial for the rapidly growing population of people with type 2 diabetes and nephropathy. Finally, the present study suggests for the first time that a lower dietary sodium intake is associated with larger cardiovascular protective effects of ARBs.

The enhanced treatment effects on albuminuria and systolic blood pressure we observed in the lowest tertile of 24-h sodium/creatinine ratio are indicators of long-term renal and cardiovascular protection. These effects are in line with previous studies on the short-term impact of dietary sodium intake in nondiabetics and diabetics, as also summarized in a recent Cochrane review,[21] and support the interpretation that a lower dietary sodium intake, rather than other patient characteristics, potentiate the treatment effects of ARBs.[6,19,21] Furthermore, in the lowest tertile of the 24-h sodium/creatinine ratio, ARB therapy caused an initial decrease in

eGFR followed by a markedly slower long-term eGFR decline compared with non-RAASi–based therapy. An initial decrease in GFR during ARB treatment in combination with a low-sodium diet has been observed in previous studies as well.[7,22] The fall is likely of hemodynamic origin owing to a reduction in intra-glomerular pressure.[23] As an increase in intra-glomerular pressure is associated with progressive renal function loss,[24] the initial decrease in eGFR can be interpreted as a sign of the therapeutic effectiveness to achieve long-term protection.[25]

Several pathophysiological mechanisms are described that may explain the blunted treatment effect of ARBs in subjects with high dietary sodium intake. Experimental and human studies have shown that a high sodium intake increases angiotensin-converting enzyme (ACE) activity in renal and vascular tissues, despite decreased plasma renin and angiotensinogen concentrations, which in turn attenuates the effect of ACE inhibition at a tissue level.[26–28] In addition, high sodium intake exerts direct harmful effects on renal tissues through activation of transforming growth factor-β.[29] Moreover, recent studies support a role of Rac-1, a transducer of cellular membrane receptor signaling, which can activate the mineralocorticoid receptor through an aldosterone-independent mechanism during high-salt conditions resulting in renal injury.[30] Hence, each of these deleterious effects may individually, or combined, offset the protective effects of RAAS inhibition during salt loading. The tendency of less of an effect or even worsening of renal and cardiovascular outcome during ARB therapy in the upper dietary sodium tertile was not statistically significant. However, the point estimates were compelling enough to warrant further studies investigating the potential underlying mechanisms, as well as its clinical relevance for renal and cardiovascular outcomes.

What could be the implications of our study? Our study demonstrates that the renal and cardiovascular protective effects of ARBs are blunted in subjects with type 2 diabetes and nephropathy in whom dietary sodium intake is excessively high. This begs for a prospective randomized controlled trial to definitively prove that restricting dietary sodium diet as adjunct to RAAS blockade improves renal and cardiovascular outcomes in chronic kidney disease. Until further data are available, we advocate avoiding high dietary sodium intake and recommend adherence to the guideline-recommended target of salt intake of 5–6 g per day. To achieve such a change in salt intake, a concert effort of policy makers, physicians, and patients is required. In this respect, self-management is an important tool to stimulate patients to change their dietary sodium intake. Proper education directed to the individual needs of the patient, self-monitoring of dietary intake, and engaging social support from relatives have been shown to be useful to help make and maintain changes in dietary intake.[31]

We estimated sodium intake from 24-h sodium excretion. The use of urinary sodium excretion is a proxy for sodium intake, but is considered more reliable than food questionnaires. We used the average sodium excretion during follow-up for our main analyses, as it is a more accurate reflection of the actual sodium intake of a patient than measuring sodium excretion at a single time point. The results of the sensitivity analyses using only baseline sodium intake, however, showed a trend similar to our main analyses, although the *P*-values for interaction were of borderline statistical significance. A possible explanation for the weaker association is that using only baseline urine collections has led to misclassification and bias. On the other hand, however, we cannot exclude that reverse causality can lead to follow-up data showing higher hazard ratios and stronger associations.

The current report is a retrospective analysis of randomized controlled trial data. The results can therefore only be interpreted as hypothesis generating and not testing. It could be possible that the differences in patient's characteristics across tertiles of dietary sodium intake have contributed to the enhanced effects of ARBs in the lower tertile of urinary sodium excretion. However, the greater treatment effects in patients within the lowest tertile of sodium/creatinine ratio persisted in various sensitivity analyses such those adjusting for baseline eGFR, urinary urea excretion, or albuminuria. Further, similar results were observed in analyses excluding subjects allocated to calcium channel blocker treatment in the IDNT trial. We therefore consider it less likely that other patient characteristics have contributed to the greater renal and cardioprotective effect during a liberal sodium diet. Second, 24-hour urinary sodium information was available for approximately one-third of the overall RENAAL and IDNT population, which may have influenced the precision of the estimates of the effect sizes. We estimated sodium intake from sodium excretion normalized for urinary creatinine excretion in order to account for collection errors. However, creatinine excretion also reflects body dimensions, namely muscle mass, and the normalization for urinary creatinine excretion is likely to have accounted for the larger proportion of women and lower proportion of black ethnicity in the upper tertile of sodium intake. However, the notion that similar results were observed when the population was stratified according to 24-h urinary sodium excretion alone, in addition to the finding that adjustment of the interaction between treatment and 24-h urinary sodium/creatinine ratio for gender and race did not alter the findings, indicated the robustness of the results. Finally, it should be reminded that the RENAAL and IDNT trials were protocol-driven studies, and the results can only be applied to patients who share the characteristics of these populations, i.e., patients with type 2 diabetes, nephropathy, and marked proteinuria.

In conclusion, we demonstrated that the renoprotective and cardioprotective effect conferred by angiotensin receptor blockers (losartan or irbesartan) are greater during a concomitant lower than higher sodium diet, estimated from 24-h urinary sodium excretion, in type 2 diabetic patients with nephropathy. These enhanced effects underline recent calls for population-wide intervention to reduce dietary salt intake,

particularly in patients with diabetes and nephropathy treated with angiotensin receptor blockers.

MATERIALS AND METHODS

Study design

The RENAAL and IDNT trials were two large randomized, controlled double-blind trials investigating the efficacy of an ARB (losartan in RENAAL, irbesartan in IDNT) on renal outcomes compared with placebo (on a background of conventional therapy) in subjects with type 2 diabetes and nephropathy. In addition, the IDNT trial included a calcium channel blocker (amlodipine) treatment arm. The rationale, study design, and outcomes for these trials have been previously published.[32,33] Patients randomized to study treatment were up-titrated stepwise in two periods of 4 weeks to achieve a blood pressure target of at least 135/85 mm Hg (50–100 mg losartan (RENAAL), 75–300 mg irbesartan (IDNT), or 2.5–10 mg amlodipine (IDNT)). After the end of the titration period, the dose of other antihypertensive drugs was increased or additional antihypertensive agents (but not ACE inhibitors or ARBs in RENAAL and ACE inhibitors, ARBs, or calcium channel blockers in IDNT) were added to achieve the target blood pressure.

Study participants

A total of 3228 adult patients with type 2 diabetes and nephropathy participated in the RENAAL and IDNT trials. Of these participants, 1177 (36%; 591 RENAAL participants and 586 IDNT participants) collected a 24-h urine, which allowed adequate assessment of daily sodium excretion rate. These 1177 subjects were included in the current analysis. Inclusion criteria were similar, but there were minor differences in detail for these trials. Patients who were eligible had type 2 diabetes, were aged between 30 and 70 years, and had serum creatinine levels ranging between 1.3 and 3.0 mg/dl in the RENAAL trial (with a lower limit of 1.5 mg/dl for males) and 1.0 and 3.0 mg/dl in the IDNT trial (with a lower limit of 1.2 mg/dl for males). All subjects had proteinuria, defined as 24-h urinary protein excretion >500 mg per day in the RENAAL trial and >900 mg per day in the IDNT trial. Exclusion criteria for both trials were type 1 diabetes or nondiabetic renal disease.

Follow-up and assessments

After the randomization visit, subjects were seen at 4-week intervals until 3 months, and subsequently at 3-month intervals. Serum creatinine and electrolyte levels were measured throughout follow-up. 24-h Urinary albumin, creatinine, and sodium were measured at the randomization visit and every 6 months thereafter. The abbreviated Modification of Diet in Renal Disease equation was used to estimate GFR.[34] Dietary advice during the trial was in keeping with those of the American Diabetes Association. Treatment effects were calculated on renal and cardiovascular outcomes according to tertiles of the mean sodium intake during follow-up. We selected the mean sodium intake during follow-up as it more accurately reflects the exposure of a subject to a certain sodium load during the trial than a single measure. Incontinence and erroneous 24-h urine collections are typically common in patients with diabetes as a result of diabetic neuropathy including diabetic bladder dysfunction and poor bladder emptying.[35] To normalize for possible urine collection errors and body size dimensions, we divided 24-h urinary sodium excretion by 24-h urinary creatinine excretion.[36,37] 24-h Albuminuria excretion was also normalized for 24-h urinary creatinine excretion. To establish the robustness of the analyses, we also performed all analyses according to another measure of sodium intake, namely 24-h urinary sodium excretion.

Renal and cardiovascular outcomes

The renal outcome in this analysis was defined as a composite of a confirmed doubling of serum creatinine from baseline or end-stage renal disease. The latter was defined as the need for chronic dialysis or renal transplantation. An additional definition for end-stage renal disease of a serum creatinine $\geqslant 6$ mg/dl ($\geqslant 530$ μmol/l) applied in the IDNT trial. The rate of estimated GFR decline over time was an additional outcome in both trials. The cardiovascular outcome was the original secondary outcome of both trials defined as the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure, or revascularization procedures. As both the RENAAL and IDNT trial showed that ARB treatment reduces the rate of hospitalization for heart failure, the interaction between urinary sodium excretion and ARB treatment was assessed on this end point as well. All clinical end points were adjudicated by a blinded end-point committee using rigorous guideline definitions.

Statistics

The effects of ARB treatment vs. non-RAASi–based therapy on renal and cardiovascular end points were estimated from unadjusted Cox proportional hazard models. Test for interaction in treatment effects across tertiles of 24-h urinary sodium/creatinine ratio were performed by adding interaction terms (ARB treatment assigned*sodium intake) to the relevant Cox models. For subjects who experienced more than one renal or cardiovascular event during follow-up, survival time to the first relevant end point was used in each analysis. Participants were censored at their date of death or, for those still alive, at the end of follow-up, the date of their last clinic visit before the termination of the trials. The rate of eGFR decline over time was estimated in each tertile of 24-h urinary sodium/creatinine ratio. The difference in eGFR decline between ARB and non-RAASi–based therapy was estimated by a linear mixed-effects model with random intercepts and random slopes. For the purpose of analysis, we combined the subjects assigned to calcium channel blockers with the placebo group of both trials. To ascertain the validity of this approach, a sensitivity analysis was performed excluding the patients assigned to the calcium channel blocker arm in the IDNT trial. Differences in characteristics of participating subjects among tertiles of 24-h urinary sodium/creatinine ratio were determined with one-way analysis of variance or the Kruskal–Wallis test where appropriate. Relative risk reductions are described in the text as percentage reductions ((1−hazard ratio) × 100). Differences between randomized groups in blood pressure and albuminuria at month 6 were estimated by analysis of covariance. All *P*-values were calculated from two-tailed tests with a type I error rate of 0.05. Analyses were performed using SAS 9.2 for Windows (SAS Institute, Cary, NC).

DISCLOSURE

DdZ and H-HP have received financial support from Merck & Company for their participation in the RENAAL Steering Committee. The remaining authors declared no conflict of interests.

ACKNOWLEDGMENTS

HJLH is supported by a VENI-Grant from the Netherlands Organisation for Scientific Research. This *post-hoc* analysis was funded by a grant from the Dutch Top Institute Pharma (project no. T6-202). The RENAAL trial was funded by Merck & Company. The

IDNT trial was sponsored by Bristol-Myers Squibb Institute for Medical Research and Sanofi-Synthelabo.

The corresponding author had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

SUPPLEMENTARY MATERIAL

Table S1. 24-h albuminuria and systolic blood pressure response to ARB therapy compared with non-RAASi based therapy at month 6 according to 24-h urinary sodium excretion.
Table S2. Effect of ARB versus non-RAASi in the RENAAL and IDNT trials according to sodium intake at *baseline* on renal and cardiovascular outcomes.
Figure S1. Effect of ARB treatment on the risk for renal outcomes in subjects according to tertiles of urinary sodium:creatinine ratio.
Figure S2. The effect of Irbesartan versus Amlodipine in the IDNT trial on the risk of renal and cardiovascular events according according to tertiles of urinary sodium:creatinine ratio.
Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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